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August 26, 1999

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20857

SUBJECT: Docket 99D-0529
DRAFT Guidance for Industry on Changes to an Approved NDA or ANDA

Dear Sir or Madam:

We refer to the June 28, 1999 Federal Register notice requesting comments on the draft guideline "Guidance for Industry on Changes to an Approved NDA or ANDA," Docket No. 99D-0529. As discussed at the August 19, 1999 FDA/Industry meeting on this topic, we concur with PhRMA's and PDA's assessment that the document, while progressive in some sections, does not meet the intent of Congress in the manufacturing changes sections of FDAMA, to relieve regulatory burden. We urge the Agency to incorporate the industry suggestions identified and discussed at the August 19 meeting into a final, comprehensive document, rather than focusing on meeting an imposed deadline with a guidance document that does not address the Congressional intent of this section of FDAMA. Our general and specific comments are appended, a copy of which will be e-mailed to Nancy Sager, as requested at the meeting.

We thank the Agency for the opportunity to provide comments on this draft guidance and look forward to a continuing dialog as the Agency finalizes its guidance and rule on this topic. Please do not hesitate to contact me at (609) 730-3081 if you have any questions.regarding our comments.

Sincerely,

Sheila Alexander
Asst. Director, Technical Regulatory Affairs

99D-0529

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General Comments
We concur with PhRMA's and PDA's recommendation that the term "validate," used throughout the document, should be revised to "assess," "evaluate" or "confirm," to avoid potential confusion with the cGMP definition of "validation," which would not apply here.

We also urge the Agency to commit to minimize the time period between issuance of the final guidance document and corresponding revisions to tne SUPAC guidelines, to avoid inconsistencies between the documents.

Line 56 - "extraordinary hardship" and expedited review
As discussed at the FDA/Industry meeting, please consider adding mandatory vendor-imposed changes (without sufficient reaction time) to the list of "not reasonably foreseen" events. An example of such an event is a vendor's decision to discontinue manufacturing a certain resin and close its manufacturing plant, without an alternative source/site.

Line 72 - "FDA may order the manufacturer to cease distribution"
FDA should consider the implications of this action on availability of unique or life-saving drugs.

Line 82, 778, 782 - comparability protocols
As discussed at the FDA/Industry meeting, we urge tne Agency to consider a CBE-30, rather than PAS filing mechanism for these protocols, based on their expected brevity for review. Also, we support the position that such protocols should be fileable for approval in *original* NDAs, in addition to post-approval filings. We would like to operate with the understanding that, if a relevant protocol is subsequently published in an official compendia or Agency document (guidance, et al), the less burdensome protocol may be applied. Finally, we would welcome the Agency's involvement in drafting "common" comparability protocols, so consistent requirements are imposed on all sponsors. Alternatively, Agency guidance on comparability protocol format/content would be helpful.

Line 89 - listing all CMC changes in the supplement/annual report cover letter
We recommend that this requirement be more flexible, such that the summary of changes may appear in an introductory section of a supplement or at the beginning of the CMC section of an annual report. We note that annual report cover letters are typically very brief and, often, are not intended to include a comprehensive summary of the content of the annual report. Such a requirement would result in the cover letter becoming a voluminous document, which simply duplicates the information in the annual report itself.

Line 90-96 - cGMP obligations
It is our opinion that this paragraph is not appropriately included in the guidance, as it is part of general GMP regulations - not 21 CFR 314.70.

Line 187 - changes in quantitative composition, including inactive ingredients
We note that the quantitative levels of inactive ingredients are covered in certain SUPAC guidances and list percentage ranges over which the components can be varied. For example, a change of up to 5% in an excipient is considered a minor change in SUPAC-SS and may be reported in the Annual Report. This guidance should follow the standards set by SUPAC in this regard.

Line 285 - site change for DS manufacture, with unchanged process and satisfactory cGMP

Under current 21 CFR 314.70(c)(3), a move to a site on a different campus for the manufacture or processing of any drug product, in-process material or drug substance that is not otherwise listed as a major change is currently a CBE. A change to CBE-30 represents an unnecessary delay in implementing such a change and an increased reporting requirement over the existing regulations. Therefore, we suggest that this not be listed as a CBE-30 change.

Line 333 - change in floor plan
This information is not typically part of the NDA filing, but subject to Field inspection. Therefore, we do not believe it is warranted to identify such changes in the annual report.

Line 335 - manufacturing area improvements
This example is vague and subject to misinterpretation. Please clarify or delete.

Line 357, 370 - "changes may affect product sterility assurance"
As discussed at the FDA/Industry meeting, we suggest clarifying that these are changes with "potential *negative* (or adverse) impact on sterility."

Line 374 - PAS for addition, deletion or substitution of aseptic processing steps
Addition or substitution of aseptic processing steps may not negatively impact sterility assurance, and in fact could enhance sterility assurance. In these cases, PAS would not be warranted.

Line 401 - PAS for filter size/material changes
Consider that these changes may be CBE-30, based on accumulation and submission of appropriate comparability data to existing filter.

Line 414 - PAS for DS synthesis change
Changes in DS synthesis route, which occur prior to the formation of key intermediates, should not be regarded as major changes, since the potential to impact the quality, strength, identity and purity of the final product is low.

Line 423 - PAS for inks not currently used in CDER-approved products
FDA should develop a list of inks currently used in CDER-approved products which, if used by a manufacturer, would not require a prior approval supplement.

Line 540-556 - CBE-30 for relaxing acceptance criteria or deleting a test for raw materials, starting materials or intermediates used in DS synthesis; changed analytical procedure
Under the draft BACPAC I guidance, relaxing an acceptance criteria is considered a CBE supplement. A change to CBE-30 represents an increased reporting requirement over the existing guidance. We do not believe such a requirement is appropriate. Also, if the change is to comply with an official compendium, it should be filed in an annual report.

Line 567 - AR for change to comply with official compendium if consistent with FDA requirements and provides same or greater level of assurance....
The criteria that the change be "consistent with FDA requirements" and "provide the same or greater level of assurance" represents an increased regulatory burden over the existing 21 CFR 314.70(d)(1). In addition, it dilutes the status of the USP/NF as official US compendia. It has the potential to produce inconsistent standards for the same drug, depending on source. Finally, it can impose a competitive disadvantage to innovator firms who must comply with USP and (possibly more stringent) FDA requirements, while subsequent manufacturers may conform only with USP.

Line 584, 794-799 - tightening specifications for reference standards

Under existing CDER Guidance Documents (Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, Feb. 1987), there is no requirement for specifications for reference standards. The purification process utilized to prepare the reference standard is provided in the original NDA, and is not typically updated thereafter. This section of the proposed rule represents an increased reporting requirement.

Line 619 - PAS for change to ink/adhesive that has not been approved by CDER
FDA should develop a list of inks and adhesives currently used in CDER-approved products, with corresponding packaging components for which they are used.

Line 647 - CBE-30 for change in secondary packaging components, not otherwise listed
Secondary packaging components (e.g., cartons), not intended to provide additional DP protection, are typically not described in the NDA. As such, they should not be subject to this filing requirement.

Line 677-682 and 693-694 - AR for change/addition of cap liner or seal; change in antioxidant, stabilizer or mold releasing agent
We agree with the Agency regarding this clarification and welcome the regulatory relief.

Line 695-700 - AR for change to blister package that provides same or better protective properties, if CDER-approved for same type product
We agree with the Agency regarding this clarification and welcome the regulatory relief.

Line 711-713 - AR for change in secondary packaging components, not intended to provide additional protection to the DP
Secondary packaging components (e.g., cartons), not intended to provide additional DP protection, are typically not described in the NDA. As such, they should not be subject to this filing requirement.

Line 776-777 - PAS for "changes that may affect product sterility assurance"
As stated above, we suggest that this be clarified to "changes which may *negatively* (or adversely) impact sterility assurance."